Roles of long non-coding RNA SNHG16 in human digestive system cancer (Review)

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Abstract. The incidence of tumors in the human digestive system is relatively high, including esophageal cancer, liver cancer, pancreatic cancer, gastric cancer and colorectal cancer. These malignancies arise from a complex interplay of environmental and genetic factors. Among them, long non-coding RNAs (lncRNAs), which cannot be translated into proteins, serve an important role in the development, progression, migration and prognosis of tumors. Small nucleolar RNA host gene 16 (SNHG16) is a typical lncRNA, and its relationship with digestive system tumors has been widely explored. The prevailing hypothesis suggests that the principal molecular mechanism of SNHG16 in digestive system tumors involves it functioning as a competitive endogenous RNA that interacts with other proteins, regulates various genes and influences a downstream target molecule. The present review summarizes recent research on the relationship between SNHG16 and numerous types of digestive system cancer, encompassing its biological functions, underlying mechanisms and potential clinical implications. Furthermore, it outlines the association between SNHG16 expression and pertinent risk factors, such as smoking, infection and diet. The present review indicated the promise of SNHG16 as a potential biomarker and therapeutic target in human digestive system cancer.

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Abbreviations: ARDS, acute respiratory distress syndrome; ceRNAs, competing endogenous RNAs; CRC, colorectal cancer; CT, computerized tomography; CTCF, CCCTC binding factor; DM, diabetes mellitus; EC, esophageal cancer; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; GC, gastric cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDI, human development index; lncRNA, long non-coding RNA; miRNAs, microRNAs; PC, pancreatic cancer; SNHG16, small nucleolar RNA host gene 16; T2DM, type 2 diabetes mellitus; TEAD1, TEA domain transcription factor 1

Key words: small nucleolar RNA host gene 16, human digestive system cancer, ceRNA, risk factors, biomarker

Contents

1. Introduction

In 2020, human digestive system tumors, mainly esophageal cancer (EC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), gastric cancer (GC) and colorectal cancer (CRC), resulted in >5 million new cases and ~4 million cancer deaths worldwide. These malignancies are associated with personal suffering, and impose a substantial economic burden on patients, families and society (1,2). For example, the median medical expenditure per patient with EC in China increased from 6,851 to 57,554 CNY during 1996-2013, with an average growth rate of 11.89% (3). From a societal perspective, the costs associated with CRC in Europe reached ~19 billion

EUR in 2018 (4). In the past few decades, although modern cancer treatments, including surgical treatment, chemotherapy, radiotherapy, immunotherapy, targeted therapy and traditional Chinese medicine, have markedly improved the quality of life of patients, limited effects have been achieved on patients with advanced or metastatic cancer (5-7). It is well known that the development processes of cancer are influenced by genetic and environmental factors, including environmental agents; lifestyle habits, such as a poor diet; and social behavior, such as immoderate consumption of alcohol. Various clinical trials have been conducted on targeted therapy for digestive tract cancer. Since gene mutations, such as those in the BRCA2 gene, are prevalent in PC and CRC, the development of corresponding targeted drugs has been initiated (8-10). However, these drugs still face the challenge of acquired resistance, and the efficacy of targeted therapy remains less pronounced than traditional therapy, such as chemotherapy, in some tumors. There is therefore a pressing need to identify new therapeutic targets to provide theoretical support for the clinical treatment of digestive system cancer.

Long non-coding RNAs (lncRNAs) are single-strand RNA molecules >200 nucleotides long, which are transcribed by RNA polymerase II and lack protein-coding ability (11). Extensive research has underscored the substantial impact of lncRNAs on the development, proliferation, migration and prognosis of various types of cancer. These lncRNAs interact with target genes at the transcriptional level, regulating a series of biological processes, such as histone modification and chromatin remodeling. They also function as competing endogenous RNAs (ceRNAs) that interact with microRNAs (miRNAs), which are ~22 nucleotides long (11-13). For example, lncRNA BC069792 acts as a ceRNA sponge to interact with miR-658 and miR-4739, and increases the expression of the target gene KCNQ4, leading to AKT phosphorylation, and subsequently to inhibition of the proliferation and invasion of breast cancer *in vitro* and *in vivo* (14).

Small nucleolar RNA host gene 16 (SNHG16) is a member of the SNHG family that is located on human chromosome 17q25.1 and consists of four exons. SNHG16 was initially identified as a potent oncogenic factor and has been reported to promote the progression of neuroblastoma (15). In addition, SNHG16 has been recognized as non-coding RNA that is expressed in aggressive neuroblastoma (15). Numerous studies have further revealed that SNHG16 is extensively involved in the complex molecular regulatory network of various types of human cancer (16-18). For example, the knockdown of SNHG16 has been reported to suppress the proliferation and radioresistance of nasopharyngeal carcinoma cells by regulating the miR-31-5p/SFN axis (19). Furthermore, SNHG16 has been implicated as an oncogene, capable of promoting the proliferation and reducing the apoptosis of bladder cancer cells. This effect was shown to be achieved by binding and recruiting the enhancer of zeste homolog 2 (EZH2) to p21 promoter and silencing the expression of p21 (20). SNHG16 has also been shown to serve a key role in the staging, distant metastasis and poor prognosis of ovarian cancer by increasing the expression of MMP9 (21). In oral squamous cell carcinoma, the expression of SNHG16 is regulated by the transcription factor c-Myc, which recruits histone acetyltransferase and induces RNA polymerase II clearance (22). These findings suggested that SNHG16 has an important role in the progression, invasion and carcinogenesis of human cancer through upstream regulatory and downstream molecular mechanisms.

The present review begins with a concise summary of the relationship between risk factors, such as smoking, and human digestive system tumors. Then, it delves into an examination of research on the expression, biological function, related mechanisms and potential clinical significance of SNHG16 for digestive tumors, indicating a connection between SNHG16 and digestive cancers. Additionally, it outlines the association of these risk factors with SNHG16 in all reported publications. These findings collectively underscore the potential of SNHG16 as both a potential biomarker and therapeutic target in human digestive system tumors.

2. Risk factors and human digestive system cancer

Several factors have been reported to have a significant import on cancer etiology, including smoking, excessive alcohol consumption, physical activity, infection, radiation, living environment, family history, diet, disease and genomic characteristics. In the subsequent sections, the association of these risk factors with human digestive system cancers is described.

Smoking. Smoking is the leading cause of cancer, and smokers are at a higher risk of developing digestive system disorders, including digestive tract cancers (23,24). In 2019, tobacco smoking was responsible for ~203,000 deaths of patients with EC worldwide (25). Increasing evidence has demonstrated that smoking is closely associated with the development and progression of HCC, with 13% of HCC cases reported to be caused by smoking worldwide (26,27). In a statistical analysis of HCC, patients were categorized as non-smokers, current smokers and ex-smokers, according to smoking status; notably, non-smokers had higher late survival rates than current smokers and ex-smokers (28). For PC, tobacco smoking is considered a major risk factor, with former or current smokers exhibiting a higher odds ratio of 1.42-1.74 than non-smokers (24,29). A number of causative factors have been epidemiologically confirmed to have an association with PC, among which smoking shows the most positive correlation with the risk of PC and is a recognized risk factor (30-33). Furthermore, smoking has been shown to affect the prognosis of patients with PC (34). Similarly, smoking constitutes an established risk factor for CRC. Compared with 6,866 healthy individuals, 6,264 patients with CRC had a higher smoking status, suggesting a strong association between smoking and CRC evident across early- and late-stage CRC (35).

Notably, research in esophageal squamous cell carcinoma (ESCC), bladder cancer, non-small lung cancer and CRC has demonstrated that there is no correlation between SNHG16 expression and smoking (20,36-38). Specifically, in lung cancer, SNHG16 expression was not related to the clinical data of patients, including age and smoking history (39). Furthermore, a meta-analysis study indicated that SNHG16 expression was not associated with smoking (40). By contrast, in a study on CRC, Zhou *et al* revealed that smoking influenced the combination of rs7353, rs8038 and rs15278 sites located in the SNHG16 gene. In addition, through multifactor dimensionality reduction analysis, changes in the expression levels of SNHG16 were revealed to increase or decrease the risk of CRC susceptibility (41). In the

future, the association between smoking and SNHG16 expression in other types of cancer requires further research.

Excessive alcohol consumption. Similar to smoking, excessive alcohol consumption is associated with an increased risk of all digestive system tumors, including EC (24,42), HCC (43), PC (44), GC (45) and CRC (46). Nevertheless, moderate alcohol consumption has shown no association with certain types of digestive cancer, such as HCC, PC, GC and CRC (24,47,48). An Australian study revealed that the risk of ESCC was significantly increased with combined tobacco and alcohol use, surpassing >20-fold higher risk compared with non-smokers and non-drinkers (49).

In addition to smoking, Zhou *et al* (41) also revealed that drinking was a factor affecting SNHG16 single nucleotide polymorphisms and expression, thus affecting CRC susceptibility. To the best of our knowledge, the association between excessive alcohol consumption and SNHG16 expression has not been reported in other diseases.

Physical activity. Physical activity involves the use of skeletal muscles and requires energy expenditure. Numerous studies have demonstrated the association between physical activity and cancers (50-53). Physical activity can decrease the risk of EC by 19-51%, GC by 15-19% and colon cancer by 21-27% (50). In particular, high levels of physical activity, such as running and jumping rope, may decrease the risk of PC by 9-25% (50). Moore *et al* reported that high levels of physical activity decreased the risk of EC, HCC and GC by >20% (51). Kasvis and Kilgour (53) suggested that physical activity interventions may alleviate malnutrition and muscle wasting, which are common in PC. In China, a decade-long prospective study showed that CRC risk was 25% lower in the highest-level-of-activity group compared with in the lowest-level-of-activity group (52). In addition, a meta-analysis showed that a moderate-to-high physical activity level serves as a common protective factor that can significantly reduce the overall risk of digestive system cancer (54). To date, there is an absence of evidence to indicate the relationship between physical activity and SNHG16 expression, which should be explored in the future.

Infection. Evidence has suggested that bacterial infection serves a key role in tumor progression, such as in EC (55). *Porphyromonas gingivalis* is an important periodontal disease pathogen that has been detected in 61% of ESCC tissues (56). It has been suggested that EC is moderately positively associated with chronic hepatitis C virus (HCV) infection, with a combined relative risk of 1.61 (95% CI, 1.19-2.17) (57). For HCC, the most common risk factor is chronic hepatitis caused by hepatitis B virus (HBV) and HCV infection, and long-term chronic hepatitis can lead to cirrhosis and eventually develop into HCC (58). Furthermore, HBV products and HBV mutations may disrupt normal cell signaling pathways, leading to HBV-induced HCC (59). *Fusobacterium* has been identified as a potential prognostic biomarker for PC (60). A prospective study reported that patients with high concentrations of *P. gingivalis* have a higher risk of PC (61). *Helicobacter pylori*, which is found only in the human stomach, has been shown to be closely associated with GC as a separate risk factor (62,63). Substantial evidence has suggested that *H. pylori* carrying CagA and VacA virulence factors is highly associated with distal GC by promoting GC epithelial-mesenchymal transition (EMT) through disruption of the gastric tissue microenvironment (64-67). The Epstein-Barr virus infection can also cause GC, accounting for ~10% of patients with GC (68). In patients with CRC, *Escherichia coli* has been reported to contain a polyketide synthase gene that not only induces inflammation, epithelial cell damage and cell proliferation, but also encodes colibactin, which destroys DNA and ultimately leads to the formation of CRC (69). *Fusobacterium* has also been reported to be associated with the occurrence of CRC (70).

In some clinical samples of HCC, HBV infection showed no correlation with the expression of SNHG16 (71-75). In addition, in a meta-analysis by Liu *et al*, there was no association detected between SNHG16 expression and HBV infection (76). To the best of our knowledge, in other human digestive system tumors, the association between infection and SNHG16 expression has not been reported. In some cells, SNHG16 expression was upregulated in *Cryptococcus*-treated dendritic cells compared with in wild-type dendritic cells (77). In addition, *Mycobacterium tuberculosis* infection can increase the expression levels of SNHG16 in a dose- and time-dependent manner in macrophages (78).

Radiation. Radiation is a common tool in modern medicine, including ionizing radiation and radiotherapy, and is one of the main treatments for cancer (79-81). However, the disadvantages of radiation cannot be overlooked. In patients with head and neck tumors, the risk of ESCC is associated with the dose of radiotherapy (80). In addition, α-radiation emitted by plutonium is strongly associated with genetic mutations in HCC (82). Dores *et al* (83) proposed that both radiotherapy and chemotherapy can substantially increase the risk of PC in Hodgkin lymphoma survivors treated previously. In addition, Yusefi *et al* (84) showed that ionizing radiation is a possible risk factor for GC. Low-dose radiation exposure among uranium miners has been reported to be positively associated with GC (85). Computerized tomography radiation slightly increases the risk of CRC, whereas the benefits of computerized tomography (CT) radiation far outweigh the risks (86). Notably, to the best of our knowledge, the association between radiation and SNHG16 expression has not been reported in disease.

Living environment. A study in China revealed that drinking from untreated water sources can increase the risk of ESCC by 2-fold (87). The use of polluted water containing nitrate is considered an essential risk factor for HCC (88), PC (89), GC (90) and CRC (91). Exposure to external airborne agents, such as fine particulate matter, may also increase the risk of digestive system cancer, especially EC and GC (92,93). Tsai *et al* (93) demonstrated that PM2.5 was strongly associated with the mortality of HCC, which agrees with the results of another study, where a strong association was detected between PM2.5 and HCC and CRC (94). A previous study reported that SNHG16 expression presented no significant differences between Intensive Care Unit (ICU)-hospitalized and non-ICU hospitalized patients (95). To the best of our knowledge, in digestive system cancer, the effect of living environment on SNHG16 expression is not known.

Family history. A number of studies have shown that a family history of cancer is strongly associated with the incidence

rate of certain types of cancer, such as EC (96), HCC (97), PC (98), GC (99) and CRC (100). Parents and siblings of a person with EC and HCC have been reported to exhibit a higher risk of developing EC and HCC. Research has found that there is a clear 'dose-response' relationship with the number of first-degree relatives of EC (97,101). Furthermore, familial inheritance is a known cause of GC (102). A positive first-degree family history of CRC and GC can reduce the risk of cancer recurrence and death compared with patients without a family history, based on a well-defined cohort enrolled in a clinical trial (103,104). Su *et al* (105) reported that people with a family history of EC had a 2-fold higher risk of developing the disease with a poorer prognosis. However, in another study, the HCC survival rate was higher in the familial cancer group than in the sporadic cancer group (106). Furthermore, individuals with a family history of CRC have been shown to have a slightly increased risk of getting PC (107).

In a study on CRC, Zhou *et al* indicated that family history affected the combination of rs7353, rs8038 and rs15278 sites of the SNHG16 gene, which increased or decreased SNHG16 expression and influenced CRC susceptibility (41). Whereas in other diseases, this relationship has not been presented.

Diet. There is a consensus on the strong association between diet and digestive system tumors. Long-term unbalanced diets, such as high-calorie hot beverages or food, can lead to esophageal epithelial cell damage and exacerbate the risk of EC (108). A number of studies have demonstrated that reducing vegetable and fruit intake, and low-fiber diets, may increase the risk of HCC and PC, and increasing the intake of salted and preserved foods and meat could increase the risk of HCC and GC (109-114). Similarly, diet also influences CRC. For example, calcium, fiber, milk, wholegrains and 2'5-hydroxyvitamin D have been shown to inhibit the development of CRC; however, consumption of a large amount of red or culinary meat can increase the risk of CRC (115,116). Furthermore, patients with CRC have been reported to be deficient in vitamin C, vitamin E and folate (117). To the best of our knowledge, the association between diet and SNHG16 expression has not been published.

Disease. Existing studies have shown that both infectious diseases and chronic inflammation may account for ~25% of carcinogenic factors (118). Reactive oxygen/nitrogen species are produced under the condition of chronic inflammation, which can cause DNA damage in various organs, thereby inducing cellular carcinogenesis (118,119). Furthermore, prolonged acid reflux can cause reflux esophagitis in the proximal esophagus and expedite esophageal carcinogenesis (120). Non-alcoholic fatty liver disease can result in a series of diseases, including steatosis accumulation, non-alcoholic steatohepatitis, inflammation, liver fibrosis and cirrhosis, which may eventually lead to HCC (121-123). Chronic pancreatitis is also a causative factor in the development of PC. Patients who have had this disease for >2 years face a 2.71-fold higher risk of developing PC (124). Chronic gastritis, one of the most common types of chronic inflammation, is considered a precursor of GC (125,126). Chronic enteritis and dysbiosis of the intestinal microflora can increase the risk of CRC (127). Notably, diabetes mellitus (DM) and obesity are risk factors for digestive system cancer, enhancing the development of EC (128), HCC (29), PC (129,130), GC (131,132) and CRC (133). For example, type 2 DM (T2DM) is often recognized as an independent risk factor for HCC, with a 2- to 4-fold increased risk in patients with T2DM compared with the general population (134).

In HCC, liver cirrhosis has been reported to not necessarily be associated with the expression of SNHG16 (71,74,75,135). By contrast, investigations into the association between portal vein tumor thrombus (PVTT) and SNHG16 expression have yielded dissimilar results. Guo *et al* (135) revealed a positive correlation between SNHG16 expression and PVTT, while another study indicated that high SNHG16 expression was independent of PVTT (136). Patients with sepsis and acute respiratory distress syndrome (ARDS) have been shown to exhibit a decline SNHG16 expression compared with those without ARDS, indicating that SNHG16 may possess a certain ability to discriminate patients with sepsis and ARDS from those without ARDS, according to the area under curve (137). Moreover, SNHG16 in patients with sepsis has been discovered to have a negative correlation with diabetes and chronic obstructive pulmonary disease history, rather than other medical history, such as hypertension (137). In addition, some studies have found that SNHG16 serves an important role in sepsis-induced acute lung injury and inflammation via an involvement in the pathogenesis of ARDS (138-140). In patients with acute ischemic stroke, SNHG16 expression was revealed to be negatively related to comorbidities, such as hyperlipidemia and disease severity (141). SNHG16 has been shown to be upregulated in unilateral ureteral obstruction-induced renal fibrotic tissues of mice (142).

Genomic characteristics. Cancer is a multi-stage process disease and its occurrence is not only disturbed by external factors, but also by intrinsic genetic mutations. The occurrence of genetic mutations serves an important role in the development of digestive system tumors. KRAS, a proto-oncogene, affects the cellular proliferation and differentiation in digestive system cancer, and can influence the prognosis of these patients (143,144). KRAS mutations have been found in ~85% of patients with PC and ~45% of patients with CRC (145). Similar results have been reported regarding tumor suppressor genes. Mutations in the TP53 gene usually occur in the early stages of GC and can accelerate the progression of GC (146). In HCC, TP53 mutations have been detected in circulating exosomal DNA and are associated with the prognosis of patients (147). APC mutations are associated with tumorigenesis, affecting the overall survival of patients with CRC (148,149). A previous meta-analysis showed the neutral function of PIK3CA mutations on the overall survival and progression-free survival of patients with CRC (144). Specifically, individuals who have both genetic and lifestyle-related risks have a ~190 times higher risk of ESCC than those without these risks (150). To the best of our knowledge, the association between genomic characteristics and SNHG16 expression has not yet been presented.

Epigenetic influences, such as DNA methylation, histone modifications and non-coding RNA regulation, are also important factors (151). The role of lncRNA in the process of cancer development and progression cannot be overlooked. A number of studies have shown that SNHG16 is a key factor in

the process of digestive system cancer, including promoting the proliferation of cancer cells, resisting cancer therapeutic drugs and enhancing cancer cell invasiveness. The possible mechanisms and functional characterization of SNHG16 in human digestive system cancer are presented in Fig. 1 and Table I, respectively. Furthermore, the association between SNHG16 expression and clinicopathological characteristics is summarized in Table II.

3. SNHG16 and human digestive system cancer

SNHG16 and EC. EC is one of the major cancer types worldwide, ranking 7th (3.1%, 604,100 new cases) and 6th (5.5%, 544, 076 deaths) among all types of cancer in terms of incidence and mortality rate, respectively (2). Its incidence and mortality rates vary between geographic regions (2). For example, due to economic underdevelopment and dietary habits, the burden of EC is higher in East Asia with a predominance of patients with ESCC (2). Studies have shown that SNHG16 expression is upregulated in EC, and is closely associated with tumor stage, lymph node metastasis and clinical stage (36,152-154). The knockdown of SNHG16 has been reported to suppress the proliferation and invasion, and promote apoptosis by reducing the expression of β-catenin, cyclin D1 and c-Myc protein in EC-1 and Eca-109 cells (36). In addition, Zhang *et al* verified by reverse transcription-quantitative PCR (RT-qPCR) that the expression levels of SNHG16 were upregulated in EC tissues or cells compared with those in normal tissues or cells ($P<0.01$). This previous study also observed that the disruption of SNHG16 expression suppressed proliferation, promoted apoptosis and inhibited EMT through the miR-140-5p/ZEB1 axis *in vivo* and *in vitro* (152). In another study on ESCC, the expression of SNHG16 was revealed to be associated with tumor differentiation and T stage, and increased expression of SNHG16 could promote ESCC growth and metastasis. The underlying mechanism may be that SNHG16 binds to and recruits EIF4A3 to modulate RhoU expression, thereby enhancing the stability of RhoU mRNA (154). Zhang *et al* (153) demonstrated that SNHG16 acts as a sponge of miR-802 to upregulate PTCH1 and activate the Hedgehog pathway, thus facilitating EC proliferation and self-renewal.

These results show that the upregulation of SNHG16 may be strongly associated with the development of ESCC, suggesting the potential utility of SNHG16 as a marker for ESCC. These insights offer novel avenues for the clinical management of ESCC.

SNHG16 and liver cancer. HCC is one of the most common malignancies worldwide, accounting for 4.7% (906,000 new cases) of all new cancer cases and 8.3% (830,000 deaths) of all cancer-related mortalities. HCC is ranked as the 6th most commonly diagnosed cancer and the 3rd leading cause of cancer-related deaths (2). In most studies, SNHG16 has been considered a proto-oncogene of HCC, and RT-qPCR has been used to detect the expression of SNHG16 in HCC tissues and corresponding non-tumor tissues. The results showed that the expression levels of SNHG16 in HCC samples were much higher than those in matched non-tumor samples, and upregulation of SNHG16 expression was highly associated with poor prognosis and tumor stage of HCC. Furthermore, the patients with advanced-stage HCC exhibited a significantly higher SNHG16 expression level than the patients with early-stage HCC (72,155). Moreover, the high expression of SNHG16 has been shown to be associated with the tumor size, TNM stage and vascular infiltration of patients with HCC (74). SNHG16, as a ceRNA, can target STAT3 and GALNT1 through sponging miR-4500 in Huh7 cells and human umbilical vein endothelial cells (HUVECs), respectively, to promote proliferation, metastasis and invasion of Huh7 cells, and enhance angiogenesis of HUVECs (72,156). In addition, through regulating miR-195, miR-17-5p/P62, miR-302a-3p/FGF19 and miR-186 expression, SNHG16 can inhibit the proliferation, migration and invasion of HepG2 and Hep3B cells (71,73,155,157). Overexpression of SNHG16 may also affect the G_2/M transition of HCC cells by regulating CDC25B expression through sponging miR-let-7b-5p (158). A previous study reported that SNHG16 is upregulated in sorafenib-resistant tumor tissues and cells, and that the overexpression of SNHG16 can enhance sorafenib resistance in HCC (74). By contrast, when the expression of SNHG16 is suppressed, sorafenib resistance disappears (135). Jing *et al* (159) also suggested that SNHG16 may enhance HCC autophagy via the miR-23b-3p/EGR1 axis and protect HCC from sorafenib resistance. In addition, it has been reported that SNHG16 can be phagocytized by telocytes and can mediate telocytes to promote HCC cell metastasis by regulating the miR-942-3p/MMP9 axis (160). Furthermore, Hu *et al* (75) demonstrated that the overexpression of SNHG16 promotes TRAF6 expression by sponging miR-605-3p, activates NF-κB and exacerbates the development of HCC. Specifically, the activated NF-κB can enhance SNHG16 promoter activity, forming a positive SNHG16/NF-κB feedback loop that further worsens HCC (75). The overexpression of SNHG16 has also been shown to be associated with tumor recurrence and poor prognosis after surgery, and mechanistic analyses suggested that SNHG16 markedly activates the extracellular matrix-receptor interaction pathway (136).

Studies have demonstrated that SNHG16 regulates a large lncRNA-miRNA-mRNA network in HCC, and is closely associated with the infiltration of immune cells, the release of immunomodulatory factors and the expression of chemokines in tumor tissues (161-163). Notably, UBE4B and SEMA3F may promote HCC progression regulated by their upstream SNHG16/miR-22-3p and SNHG16/let-7c-5p axes, respectively (163,164). Liu *et al* (76) revealed that SNHG16 can be used as a potential biomarker for patients with HCC with a poor prognoses. In summary, SNHG16 may be upregulated in HCC and can promote HCC development. Notably, a previous study presented the opposite argument, suggesting that SNHG16 expression may be reduced in HCC tissue compared with in normal liver tissue, and that overexpression of SNHG16 could decrease the proliferation of Hep3B and Huh7 cells, and inhibit HCC development and chemoresistance via sponging miR-93 (165). This discrepancy in findings may stem from the diverse dysregulation patterns of SNHG16 in human cancer, with its expression being either upregulated or downregulated. Such variations could be influenced by the specific cancer types, their anatomical locations and the microenvironments involved (165). This discrepancy prompts further research into the role of SNHG16 in HCC.

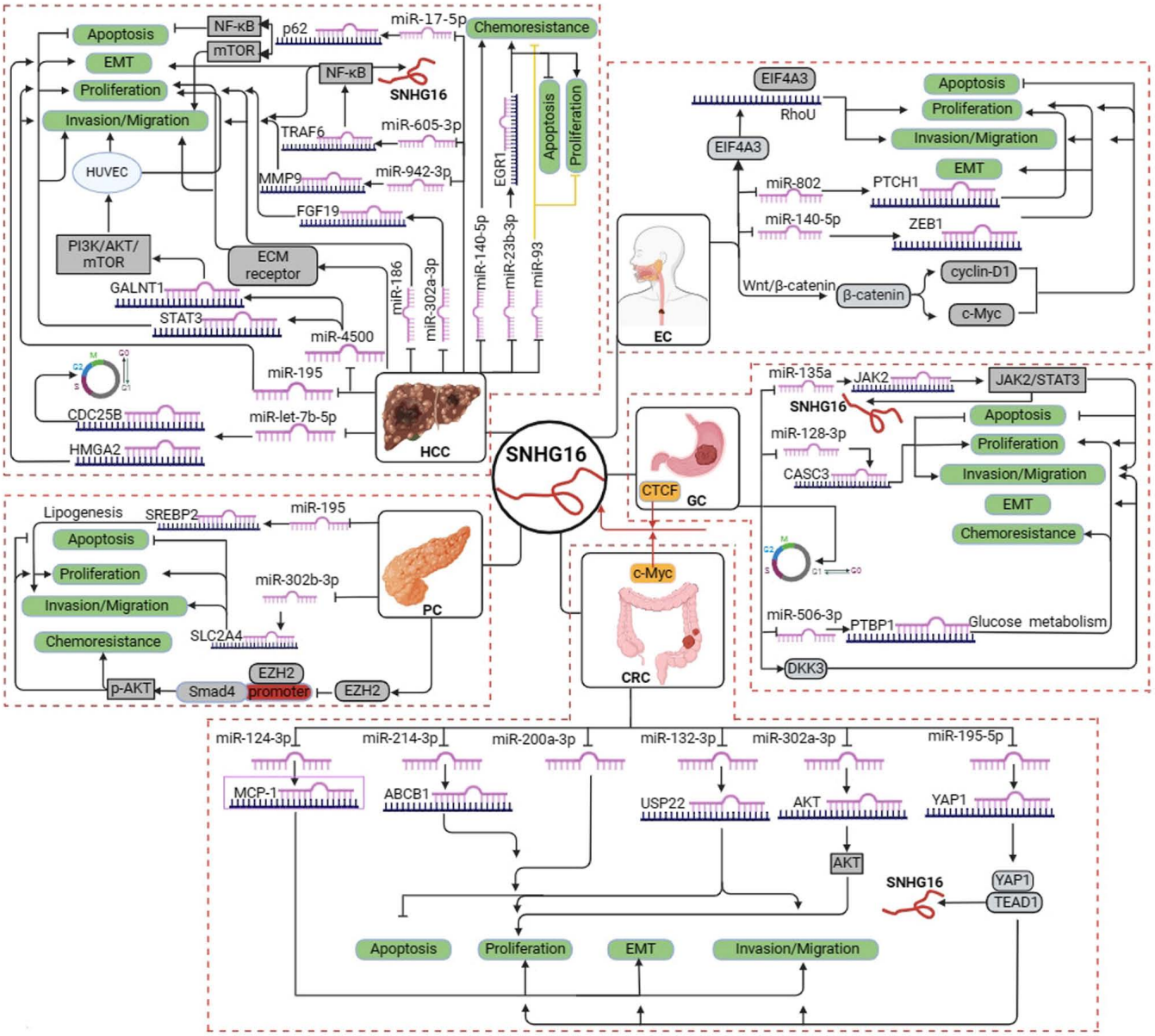

Figure 1. Potential regulatory mechanisms of SNHG16 in human digestive system cancer. EC, esophageal cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; GC, gastric cancer; CRC, colorectal cancer; SNHG16, small nucleolar RNA host gene 16.

SNHG16 and PC. PC is one of the most serious malignancies of the digestive system. Due to its poor prognosis, PC accounts for almost as many deaths (466,000) as cases (496,000) in the world, and is the 7th leading cause of cancer death in both men and women (2). Similar to EC, the incidence rate of PC is 4-fold and 5-fold higher in high human development index (HDI) countries compared with in low HDI countries (2). Studies have shown that the expression levels of SNHG16 are upregulated in PC tissue compared with those in normal tissue (166,167). Altering the expression of SNHG16 may inhibit the adipogenesis of AsPC-1 and PANC-1 cells through the miR-195/SREBP2 axis (168). Inhibition of SNHG16 expression can result in the release of miR-302b-3p, which inhibits SLC2A4 expression and promotes apoptosis in PC cells (166). Overexpression of SNHG16 has also been reported to be closely associated with gemcitabine resistance in PC cells. SNHG16 can interact with EZH2, suppressing SMAD4 expression via EZH2 binding to the SMAD4 promoter (167). Downregulation of SMAD4 has a reduced ability to inhibit AKT phosphorylation, thereby promoting gemcitabine resistance in PC cells (167). These findings suggested that SNHG16 may serve a critical role in the development of PC and that it could be regarded as a marker of poor prognosis in PC.

SNHG16 and GC. GC remains an important type of cancer worldwide, and is considered the 5th most frequent malignancy (5.6%, >1,000,000 new cases) and the 4th most common cause of death (7.7%, ~769,000 deaths) among oncological patients (2). The region with the highest age-standardized incidence rate is Eastern Asia, followed by Central and Eastern Europe (2). The expression of SNHG16 is significantly associated with the depth of infiltration, lymph node metastasis, TNM stage, histological differentiation and PTBP1 expression of GC (169,170). Knockdown of SNHG16 can significantly

Table I. Functional characterization of SNHG16 in human digestive system cancer.

A, EC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Han, 2018	128	Up	HEEC, EC-1, ECa-109, TE-13, TE-1	Up	β-catenin, cyclin-D1, c-Myc	Promote	Inhibit	Promote	NA	NA	NA	NA	(36)
Zhang, 2018	68	Up	HEEC, kyse-30, kyse-70, Eca109, EC9706, TE1	Up	miR-140-5p, ZEB1	Promote	Inhibit	Promote	NA	kyse-70 (kd-SNHG16)	BALB/c athymic nude mice	Inhibit	(152)
Ren, 2022	55	Up	HET-1A, Eca109, KYSE30, KYSE140, KYSE410	Up	EIF4A3, RhoU	Promote	Inhibit	Promote	NA	Eca-109 (oe-SNHG16 and kd-SNHG16)	BALB/c nude mice	Promote (oe); inhibit (kd)	(154)
Zhang, 2022	NA	NA	EC9706, KYSE150	Up	miR-802, PTCH1	Promote	NA	NA	NA	EC9706 (kd-SNHG16)	BALB/c nude mice	Inhibit	(153)

B, HCC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Xie, 2019	40	Up	LO2, HepG2, Huh7, SMMC7721, Hep3B, Bel7402	Up	miR-195	Promote	NA	Promote	NA	HepG2 (kd-SNHG16)	BALB/c nude mice	Inhibit	(155)
Lin, 2019	88[a]	Up	LO2, Huh7, SMMC721, HepG2, MHCC-97H	Up	miR-4500, E-cadherin, STAT3, N-cadherin	Promote	Inhibit	Promote	NA	NA	NA	NA	(72)
Ye, 2019	103	Up	LO2, HepG2, SK-hep1, Huh7, HCCLM3	Up	miR-140-5p	NA	NA	NA	Promote	HepG2 (kd-SNHG16)	Nude mice	Inhibit	(74)

Table I. Continued.

B, HCC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Li, 2021	23	Up	LO2, Huh7, HepG2, MHCC97H, MHCC97L	Up	miR-4500, GALNT1	Promote	NA	Promote	NA	Huh7 (kd-SNHG16)	BALB/c nude mice	Inhibit	(156)
Zhong, 2020	108	Up	LO2, Huh7, HepG2, SMCC7721, QGY-7703	Up	miR-17-5p, p62	Promote	Inhibit	Promote	NA	HepG2 (oe-SNHG16 and kd-SNHG16)	Athymic nude mice	Promote (oe); inhibit (kd)	(71)
Chen, 2019	50	Up	LO2, Hep-3B, Huh7, PLC, Sk-hep-1, SMMC-7721	Up	miR-186, ROCK1	Promote	NA	Promote	NA	Hep-3B (oe-SNHG16), Sk-hep-1 (kd- SNHG16)	BALB/c nude mice	Promote (oe); inhibit (kd)	(73)
Li, 2019	34	Up	LO2, Huh7, HepG2, SMMC7721, SK-Hep1, Hep3B	Up	miR-302a-3p, FGF19	Promote	NA	NA	NA	NA	NA	NA	(157)
Li, 2020	47	Up	LO2, MHCC97H, Huh7, SMMC7721, Hep3B, HepG2	Up	let-7b-5p, CDC25B, CDK1, HMGA2	Promote	Inhibit	Promote	Promote	Huh7 (kd-SNHG16)	BALB/c nude mice	Inhibit	(158)
Guo, 2019	61	Up	LO2, SK-Hep-1, Huh7, Hep3B, HepG2	up	NA	Promote	Inhibit	Promote	Promote	NA	NA	NA	(135)
Jing, 2020	40	Up	Hep3B	Up	miR-23b-3p, EGR1	Promote	Inhibit	NA	Promote	Hep3B (kd-SNHG16)	NOD/ SCID male mice	Inhibit	(159)
Xu, 2023	88	Up	LO2, MHCC97, HCCLM3	Up	miR-942-3p, MMP9	NA	NA	Promote	NA	MHCC97 (kd-SNHG16)	Nude mice	Inhibit	(160)
Hu, 2020	78	Up	LO2, HCCLM3, MHCC97L, MHCC-97H, Hep3B, HepG2	Up	miR-605-3p, TRAF6, NF-κB	NA	NA	Promote	NA	HCCLM3 (kdSNHG16) HepG2 (kd-SNHG16)	Nude mice	Inhibit	(75)

Table I. Continued.

B, HCC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Zhang, 2022	158	Up	LO2, SMMC-7721, HepG2, Hep3B, MHCC-97L, MHCC-97H, HCCLM3, Huh7, BEL-7402, PLC/ PRF/5, SK-Hep1	Up	ECM-receptor	Promote	NA	Promote	NA	NA	NA	NA	(136)
Xu, 2018	43	Down	THLE2, THLE3, Hep3B, Huh7, SNU398, SNU423, SNU429, Hep3G2, SK-HEP-1, PLC/ PRF/5	Down	miR-93	Inhibit	NA	NA	Inhibit	Huh7 (oe-SNHG16)	Female athymic nude mice	Inhibit	(165)

C, PC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Yu, 2019	NA	NA	HPDE6-C7, AsPC-1, Panc-1, BxPC-3, SW1990	Up	miR-195, SREBP2	Promote	NA	Promote	NA	NA	NA	NA	(168)
Xu, 2021	30	Up	HPY-Y5, BxPC3, Panc-1	Up	miR-302b-3p, SLC2A4	Promote	Inhibit	Promote	NA	NA	NA	NA	(166)
Yu, 2022	350	Up	HPDE, SW1990, PANC-1, ASPC-1, BxPC3	Up	EZH2, Smad4	Promote	Inhibit	NA	Promote	NA	NA	NA	(167)

Table I. Continued.

D, GC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Ding, 2022	55	Up	GES-1, AGS, BGC-823, MKN-45, MGC-803, SGC-7901	Up	miR-506-3p, PTBP1	Promote	Inhibit	NA	Promote	AGS	Nude mice	NA	(169)
Lian, 2017	122	Up	GES-1, AGS, BGC-823, MGC-803, SGC-7901, MKN45	Up	NA	Promote	Inhibit	Promote	NA	MGC-803 (kd-SNHG16)	BALB/c nude mice	Inhibit	(170)
Zhao, 2022	60	Up	GES-1, AGS, SGC-7901, BGC-823	Up	c-Myc, P53, P21, P27, cyclin-E1/A2/ D1, cdk2/6	Promote	Inhibit	Promote	NA	NA	NA	NA	(171)
Zhou, 2019	20	Up	AGS, HGC27	NA	DKK3	Promote	NA	Promote	NA	NA	NA	NA	(172)
Yang, 2022	60	Up	RGM-1, GIST882, GIST48, GIST430, GIST-T1	Up	miR-128-3p, CASC3	Promote	Inhibit	Promote	NA	GIST882 (kd-SNHG16)	BALB/c nude mice	Inhibit	(173)
Wang, 2019	32	Up	GES-1, BGC823, MGC803, MKN45, SGC7901	Up	miR-135a, JAK2, STAT3	Promote	Inhibit	Promote	NA	NA	NA	NA	(174)

E, CRC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Li, 2019	56	Up	CCC-HIE-2, CaCO-2, SW480, HCT116, LoVo	Up	miR-200a-3p	Promote	NA	Promote	NA	LoVo (oe-SNHG16)	Male BALB/c nude mice	Promote	(38)

Table I. Continued.

E, CRC

First author, year	Clinical sample		Cellular level			Functional role				Animal level			(Refs.)
	Sample size	Expression in tissue	Cell lines	Expression in cancer cells	Related genes	Proliferation	Apoptosis	Invasion/ Migration	Chemoresistance	Name of cell line injected into the animals	*In vivo* model	Effect on tumors	
Chen, 2022	120	Up	FHC, SW480, HCT116, DLD-1, LoVo	Up	miR-124-3p, MCP-1	Promote	Inhibit	Promote	NA	SW480 (kd-SNHG16)	Nude mice	Inhibit	(176)
Tan, 2022	20	Up	NCM460, HCT116, HT29, SW480, SW620, CaCo2	Up	miR-214-3p, ABCB1	Promote	Inhibit	NA	NA	HCT116 (kd-SNHG16)	Male BALB/c nude mice	Inhibit	(177)
He, 2020	50	Up	CCD841 CoN, SW480, SW620	Up	miR-132-3p, USP22	Promote	Inhibit	Promote	NA	SW620 (kd-SNHG16)	Male BALB/c nude mice	Inhibit	(178)
Ke, 2020	NA	NA	HCT116, CaCo-2	NA	miR-302a-3p, AKT	Promote	NA	NA	NA	NA	NA	NA	(179)
Christensen, 2016	606	Up	HT29, HCT116, HCT15, Colo205, DLD1, LS174T, SW620, SW480, CaCo2	NA	ASCL2, ETS2, c-Myc	Promote	Inhibit	Promote	NA	NA	NA	NA	(182)
Xiang, 2022	111	Up	NCM-460, DLD-1, HCT-116, HT-29, SW620, SW480, LoVo, CaCo2	Up	miR-195-5p, YAP1, TEAD1	Promote	NA	Promote	NA	HCT116 (kd-SNHG16)	Nude mice	Inhibit	(183)
Zhou, 2020	721	Up	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	(41)

CRC, colorectal cancer; EC, esophageal carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; kd, knockdown; NA, not applicable; oe, overexpression; PC, pancreatic cancer; PVTT, portal vein tumor thrombus; SNHG16, small nucleolar RNA host gene 16; miRNA/miR, microRNA; [a]10 samples from serum, remaining samples from tissue.

Table II. Association between SNHG16 expression and clinicopathological characteristics in human digestive system cancer.

A, EC

	Expression of SNHG16 and clinical features																
First author, year	Sex	Age	Smoking status	Degree of tumor differentiation	Tumor size	Overall survival	Invasion depth	Lymph nodes metastasis	Tumor stage	Histological grade	Clinical stage	Tumor location	HBV infection	PVTT	Liver cirrhosis	Macrovascular invasion	(Refs.)
Han, 2018	-	-	-	/	-	++	-	++	+	-	+	/	/	/	/	/	(36)
Ren, 2022	+	-	/	+	-	/	/	-	-	/	/	-	/	/	/	/	(154)

B, HCC

	Expression of SNHG16 and clinical features																
First author, year	Sex	Age	Smoking status	Degree of tumor differentiation	Tumor size	Overall survival	Invasion depth	Lymph nodes metastasis	Tumor stage	Histological grade	Clinical stage	Tumor location	HBV infection	PVTT	Liver cirrhosis	Macrovascular invasion	(Refs.)
Xie, 2019	-	-	/	/	-	/	/	+	+	/	/	/	/	/	/	/	(155)
Lin, 2019	-	-	/	/	+	+	/	++	++	/	/	/	-	/	/	/	(72)
Ye, 2019	-	-	/	-	+	/	+	/	++	/	/	/	/	/	-	/	(74)
Zhong, 2020	-	-	/	/	-	+	+	/	-	/	/	/	/	/	-	+	(71)
Chen, 2019	-	-	/	/	+	/	/	/	++	/	/	/	++	/	/	/	(73)
Guo, 2019	-	-	/	/	+	++	/	++	/	-	/	/	/	++	-	/	(135)
Hu, 2020	-	-	/	-	-	++	/	/	-	/	/	/	-	/	-	/	(75)
Zhang, 2022	-	-	/	-	-	++	/	/	/	-	/	/	/	-	/	/	(136)

C, PC

	Expression of SNHG16 and clinical features																
First author, year	Sex	Age	Smoking status	Degree of tumor differentiation	Tumor size	Overall survival	Invasion depth	Lymph nodes metastasis	Tumor stage	Histological grade	Clinical stage	Tumor location	HBV infection	PVTT	Liver cirrhosis	Macrovascular invasion	(Refs.)
Xu, 2021	-	-	/	/	+	++	/	+	/	/	-	/	/	/	/	/	(166)

Table II. Continued.

D, GC

First author, year	Expression of SNHG16 and clinical features																(Refs.)
	Sex	Age	Smoking status	Degree of tumor differentiation	Tumor size	Overall survival	Invasion depth	Lymph nodes metastasis	Tumor stage	Histological grade	Clinical stage	Tumor location	HBV infection	PVTT	Liver cirrhosis	Macrovascular invasion	
Lian, 2017	-	-	/	++	-	/	++	++	++	/	/	-	/	/	/	/	(170)
Zhao, 2022	-	-	/	-	/	/	+	-	-	/	/	/	/	/	/	/	(171)
Wang, 2019	-	-	/	/	++	++	/	/	+	/	/	/	/	/	/	/	(174)

E, CRC

First author, year	Expression of SNHG16 and clinical features																(Refs.)
	Sex	Age	Smoking status	Degree of tumor differentiation	Tumor size	Overall survival	Invasion depth	Lymph nodes metastasis	Tumor stage	Histological grade	Clinical stage	Tumor location	HBV infection	PVTT	Liver cirrhosis	Macrovascular invasion	
Chen, 2022	/	/	/	/	/	++	/	/	++	/	/	/	/	/	/	/	(176)
Tan, 2022	-	/	/	/	/	/	++	+	-	/	/	/	/	/	/	/	(177)
Xiang, 2022	-	-	/	-	-	+	-	++	++	/	/	-	/	/	/	/	(183)
Zhou, 2020	/	/	/	/	/	/	/	/	+	/	/	-	/	/	/	/	(41)

CRC, colorectal cancer; EC, esophageal carcinoma; GC, gastric cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PC, pancreatic cancer; PTVV, portal vein tumor thrombus. ++, $P<0.01$; +, $P<0.05$; -, $P>0.05$; /, not applicable. $P<0.05$ was considered statistically significant.

suppress the migration, invasion and arrest of cells in the G_1 phase, and can decrease c-Myc expression, and affect the formation of the p27/cyclin D1/CDK6, p53/cyclin E1 and cyclin A2/CDK2 complexes (169-171). A number of patients with GC develop 5-fluorouracil (5-FU) resistance, showing a higher vulnerability than parental GC cells. Notably, blocking the SNHG16/miR-506-3p/PTBP1 axis may effectively limit 5-FU-resistant GC cell originated-xenograft tumor growth under 5-FU treatment. Specifically, PTBP1 stabilizes the mRNA expression of glycolysis enzymes by directly binding to 3'UTR regions (169). In addition, it has been shown that SNHG16 can promote EMT by downregulating the WNT signaling pathway and inhibiting DKK3 expression, and can regulate β-catenin protein expression without participating in the β-catenin translocation between the cytoplasm and nucleus (172). In particular, SNHG16 activated by CCCTC binding factor (CTCF) can modulate gastrointestinal stromal tumor cell proliferation, migration, invasion and apoptosis through the miR-128-3p/CASC3 axis (173). In another study, SNHG16 was also demonstrated to be able to mediate the upregulation of JAK2 and STAT3 by sponging miR-135a to influence the proliferation, invasion and apoptosis of GC cells, with SNHG16 being regulated by phosphorylated-STAT3 directly or indirectly (174). In summary, SNHG16 may be closely related to the occurrence and development of GC, and could be a potential marker of poor GC prognosis.

SNHG16 and CRC. Notably, >1,900,000 new cases of CRC and 935,000 CRC-related deaths occurred worldwide in 2020; during this year, it was the third most common cancer, after female breast cancer and lung cancer, and it exhibited a close mortality rate to lung cancer (2). Growing evidence has suggested that the expression levels of SNHG16 are positively associated with advanced TNM stage, distant metastasis and shorter overall survival time in CRC (38,175-177). SNHG16 is mainly present in the cytoplasm, functioning as a ceRNA to regulate multiple miRNAs and target genes. Li *et al* (38) revealed that SNHG16 was associated with malignancy and poor prognosis in patients with CRC by sponging miR-200a-3p. Tan *et al* (177) indicated that SNHG16 could promote CRC proliferation by upregulating its target gene ABCB1 through interacting with miR-214-3p. He *et al* (178) concluded that SNHG16 could activate USP22 expression to promote CRC progression via absorbing miR-132-3p. Ke *et al* (179) demonstrated that SNHG16 supported colon cancer cell proliferation by targeting the miR-302a-3p/AKT axis. Chen *et al* (176) revealed that the expression of SNHG16 was higher in cancer tissues from patients than in the matched normal tissues, and was positively related to CRC grade. It was also revealed that SNHG16 may serve a contributory role in the proliferation, migration and EMT of CRC cells through the miR-124-3p/MCP-1 axis (176). Some bioinformatics analyses also reached a similar conclusion, in that SNHG16 may have an important role in CRC (175,180). In particular, SNHG16 has been reported to be closely associated with autophagy in CRC (175,181).

The expression of SNHG16 may be activated by other proteins, such as c-Myc. Christensen *et al* reported that the expression of SNHG16 is determined by Wnt-regulated transcription factors such as c-Myc in CRC (182). Specifically, knockdown of β-catenin could reduce the expression of SNHG16 and c-Myc, whereas c-Myc knockdown or overexpression could decrease or increase the SNHG16 expression, respectively (182). In a study by Xiang *et al*, the SNHG16/YAP1/TEA domain transcription factor 1 (TEAD1) positive feedback loop was detected in CRC cells (183). SNHG16 was shown to act as a ceRNA that can physically bind miR-195-5p, further regulating YAP1 expression and facilitating tumor progression. YAP1 binds to TEAD1 to form a YAP1/TEAD1 complex, which in turn binds to two sites in the promoter of SNHG16 and activates SNHG16 transcription (183).

In addition, SNHG16 polymorphisms have been shown to be significantly associated with CRC susceptibility. Research has revealed that the rs7353 site A>G of the SNHG16 gene is associated with decreased susceptibility of CRC; however, the rs8038 site G>A, rs15278 site A>G and rs15278 site G>A variations may increase CRC susceptibility (41).

SNHG16 and other types of cancer. SNHG16 has also been studied in other gastrointestinal tumors. For example, SNHG16 expression has been shown to be upregulated in cholangiocarcinoma tissues and cell lines. When SNHG16 expression was suppressed, the proliferation rate of RBE and HuCCT1 cells was reduced, whereas apoptosis was activated (184). Wu *et al* (184) also revealed that there was a potential binding site for miR-146a-5p at the 3'UTR end of GATA6 and that SNHG16 could sponge miR-146a-5p. Interfering with the expression of miR-146a-5p reversed the SNHG16 knockdown-induced apoptosis in RBE and HuCCT1 cells, whereas overexpression of GATA6 also achieved the same effect (184). These findings suggested that SNHG16 is important for the development of cholangiocarcinoma and it could be a potential target for future drug development against cholangiocarcinoma.

Neuroendocrine tumors account for a very small portion of tumors at each site; for example, the incidence of pancreatic neuroendocrine tumors was <1 case per 100,000 people/year worldwide (1), and the incidence of gastric neuroendocrine tumors was ~0.4 per 100,000 individuals in America in 2017 (185). However, as the number of patients with cancer increases, the proportion of neuroendocrine tumors has also increased, thus highlighting the need for attention to be paid to neuroendocrine tumors. Although, to the best of our knowledge, the role of SNHG16 in neuroendocrine tumors in the digestive system has not been reported, it is a valuable direction for improving the management of neuroendocrine tumors in the future.

4. Discussion and conclusion

A growing number of studies have demonstrated that tumorigenesis is caused by a combination of genetics and environmental factors. At present, environmental factors, such as diet, require attention to prevent their effects on personal health. The present review briefly summarized the relationship between risk factors and human digestive system cancer, identifying risk factors, such as smoking and diet, which may severely affect tumorigenesis. Subsequently, this review focused on outlining the role of SNHG16 in the formation

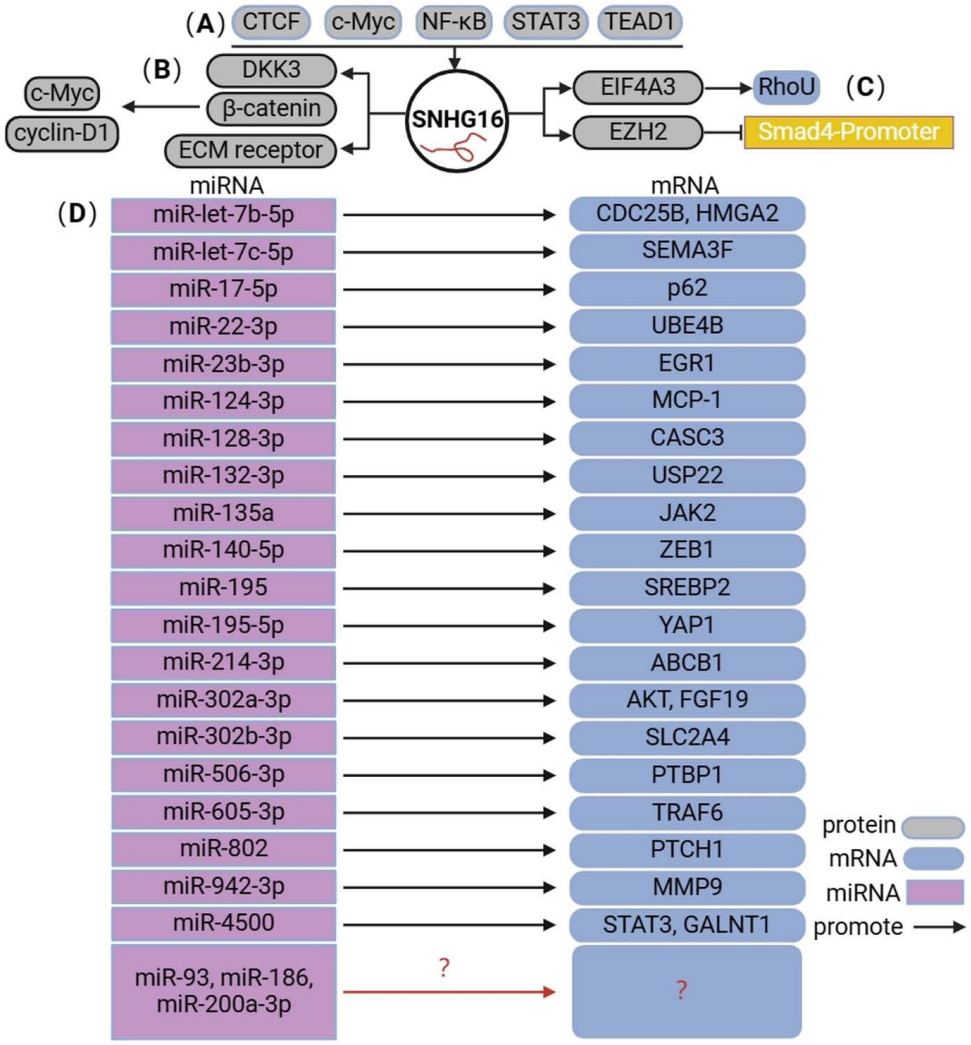

Figure 2. Upstream regulatory and downstream molecular mechanisms underlying SNHG16 in mainly human digestive system cancers. (A) SNHG16 is positively regulated by transcription factors, such as CTCF, c-Myc, NF-κB, STAT3 and TEAD1. (B) SNHG16 regulates the expression of DKK3 and Wnt/β-catenin. (C) SNHG16 could bind to and recruit EIF4A3 to regulate RhoU expression to enhance the RhoU mRNA stability, and SNHG16 also binds to EZH2 and recruits EZH2 to Smad4 promoter, subsequently suppressing Smad4 expression. (D) SNHG16 functions as a competing endogenous RNA to regulate multiple miRNAs and target genes. SNHG16, small nucleolar RNA host gene 16; miRNA/miR, microRNA.

and progression of digestive system cancer (Fig. 2). Available data have suggested that SNHG16 is strongly associated with proliferation, migration, invasion, apoptosis and prognosis in EC, HCC, PC, GC and CRC.

Upregulation of SNHG16 is clinically important, and is associated with tumor stage, lymph node metastasis and tumor size. It may be used as a novel diagnostic or prognostic biomarker for human digestive system tumors (Table II). For example, SNHG16 was revealed to be more highly expressed in EC tissues compared with in normal EC tissues, and similar results were observed in EC cell lines (36,152,154). In addition, overexpression of SNHG16 is strongly associated with the tumor stage, lymph node metastasis and clinical stage of EC (36). A Kaplan-Meier assay demonstrated that patients with EC and high SNHG16 expression had poorer overall survival rates than those with low SNHG16 expression (36). Notably, univariate and multivariate analyses have revealed that SNHG16 expression may be considered an independent predictor for the overall survival of patients with EC (36). In a number of studies, SNHG16 expression has been reported to be higher in HCC tissues or cells than in normal HCC tissues or cells (71-75,135,156-160); however, a study by Xu *et al* demonstrated that SNHG16 was significantly downregulated in both HCC tissues and cells (165). Clinical data have revealed that SNHG16 expression may be closely associated with tumor size, lymph node status and TNM stage, and enhanced SNHG16 expression could be related to advanced stages and short overall survival of patients with HCC (72,74,135). Multivariate analysis indicated that SNHG16 expression was an independent prognostic factor of HCC. Notably, some studies have reported that tumor size is not affected by SNHG16 expression, which may be due to individual differences or the small size of patients (74,75,136,155). However, reduced expression of SNHG16 has been reported in mice with smaller tumor sizes (71,155). In addition to the aforementioned cancer types, similar results were also reported in GC and CRC (170,183). Generally, the aforementioned findings suggested that SNHG16 expression is strongly associated with poor diagnosis or prognosis of human digestive system tumors.

In recent years, gene therapy has emerged as a promising avenue for significantly improving the survival rate of patients with cancer (186). As aforementioned, the clinical significance and biological functions of SNHG16 may serve as a promising therapeutic target for human digestive system cancer (Table I). However, Xu *et al* (165) reported contradictory results, which may be attributed to the sites and microenvironments specific to certain cancer types. The present review of publications on SNHG16 and cancer has resulted in a consistent conclusion that SNHG16 upregulation may promote proliferation, enhance migration and invasion, inhibit apoptosis, and affect lipid metabolism and chemoresistance. For example, silencing the expression of SNHG16 could attenuate the proliferation, activate the apoptosis, and inhibit the migratory, invasive and malignant phenotype in GC cell lines. In addition, the knockdown of SNHG16 could reduce tumor volume and weight in a nude mouse human-GC xenograft model (173).

The chemoresistance of various types of cancer may also be associated with the expression of SNHG16. A series of studies on HCC have demonstrated that downregulation of SNHG16 expression can reverse sorafenib and cisplatin resistance in HCC cell lines (such as Hep3B) or xenograft models, by acting as an endogenous sponge for miR-140-5p, miR-23b-3p and let-7b-5p (74,135,158,159). However, contrasting results reported by Xu *et al* showed that upregulation of SNHG16 inhibited 5-FU chemoresistance through competitive linking to miR-93 in Hep3B and Huh7 cells (165). In PC, SNHG16 may reduce SMAD4 to induce gemcitabine resistance via EZH2-mediated epigenetic modifications (167). In GC, the SNHG16-mediated miR-506-3p/PTBP1 axis effectively led to 5-FU resistance (169). These findings suggested that decreasing SNHG16 expression may be a promising therapy for suppressing GC progression. However, to the best of our knowledge, there are not currently any clinical trials focused on SNHG16; the development of inhibitors of SNHG16 have only been researched in cancer cell lines and animal models. In addition, the association between SNHG16 expression and chemoresistance in EC and CRC has not been researched. Therefore, whether SNHG16 will become a potential target of therapy, requires further study.

In this review, we described the association between risk factors and SNHG16 expression in ESCC, HCC and CRC. Notably, smoking may not influence the expression of SNHG16 in patients with ESCC (36). Furthermore, both HBV infection and liver cirrhosis were reported to not affect the expression of SNHG16 in HCC (71-76,135). The association between PVTT and SNHG16 expression in HCC also remains controversial and is still under exploration (135,136). In CRC, the expression of SNHG16 could be regulated by risk factors, such as smoking and family history (41). To date, although smoking, excessive alcohol consumption, physical activity, infection, radiation, living environment, family history, diet, disease and genomic characteristics, are risk factors that can influence human digestive system cancer, the association between a number of risk factors and SNHG16 expression remains unclear. Therefore, further research using large-scale data will be necessary to thoroughly investigate the relationship between risk factors and SNHG16 expression.

Thus far, the upstream regulatory and downstream molecular mechanisms of SNHG16 in human digestive system cancer encompass four primary aspects (Fig. 2). i) Numerous transcription factors, including CTCF, c-Myc, NF-κB, STAT3 and TEAD1, are positively associated with SNHG16. ii) SNHG16 directly regulates the expression of downstream target genes, such as DKK3. iii) SNHG16 can bind to and recruit EIF4A3 to regulate RhoU expression and enhance RhoU mRNA stability. Meanwhile, SNHG16 also binds to EZH2 and recruits EZH2 to the SMAD4 promoter, subsequently suppressing SMAD4 expression. iv) SNHG16 can compete with miRNAs to mediate the expression of downstream target genes and activate different signaling pathways.

In conclusion, the expression of SNHG16 is associated with the clinical and pathological characteristics of patients with cancer, and regulates cell proliferation, apoptosis, invasion and metastasis through various potential mechanisms. These findings suggested that SNHG16 may serve an oncogenic role in human cancer, making it a promising target for cancer diagnosis and treatment, as well as a potential biomarker for cancer prognosis.

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Availability of data and materials

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Authors' contributions

HR, FP and LX conceptualized the study. YL, YK and LW wrote the manuscript. LW, JP, LZ and HZ searched the literatures and collected the information from the literature. YL, YK, ZY and FP designed the figures and tables. LZ and XF revised and submitted the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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